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The Science and Pharmacy

1995

MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

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Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

Table 1—Rates of Entry of Drugs in CSF and the Degrees of Ionization of Drugs at pH 7.4[7]

Drug/chemical	% binding to plasma protein	pK_a[a]	% un-ionized at pH 7.4	Permeability constant ($P\ min^{-1}$) ± S.E.
Drugs mainly ionized at pH 7.4				
6-Sulfosalicylic acid	22	(strong)	0	<0.0001
N-Methylnicotinamide	<10	(strong)	0	0.0005 ± 0.00006
5-Nitrosalicylic acid	42	2.8	0.001	0.001 ± 0.0001
Salicylic acid	40	3.0	0.004	0.006 ± 0.0004
Mecamylamine	20	11.2	0.016	0.021 ± 0.0016
Quinine	76	8.4	9.09	0.078 ± 0.0061
Drugs mainly un-ionized at pH 7.4				
Barbital	<2	7.5	55.7	0.026 ± 0.0028
Thiopental	76	7.6	61.3	0.50 ± 0.051
Pentobarbital	40	8.1	88.4	0.17 ± 0.014
Aminopyrine	20	5.0	99.6	0.25 ± 0.020
Aniline	15	4.6	99.8	0.40 ± 0.042
Sulfaguanidine	6	>10.0[b]	>99.8	0.009 ± 0.0002
Antipyrine	8	1.4	>99.9	0.12 ± 0.013
N-Acetyl-4-aminoantipyrine	<3	0.5	>99.9	0.012 ± 0.0010

[a] The dissociation constant of both acids and bases is expressed as the pK_a; the negative logarithm of the acidic dissociation constant.
[b] Sulfaguanidine has a very weakly acidic group (pK_a > 10) and two very weakly basic groups (pK_a 2.75 and 0.5). Consequently, the compound is almost completely undissociated at pH 7.4.

for all practical purposes, only the un-ionized form is said to pass through the membrane. This has become known as the *principle of nonionic diffusion*.

This principle is the reason that only the concentrations of the un-ionized form of the barbiturates are plotted in Fig 9.

For the purpose of further illustrating the principle, Table 1 is provided.[7] In the table, the permeability constants for penetration into the cerebral spinal fluid of rats are higher for un-ionized drugs than for ionized ones. The apparent exceptions—barbital, sulfaguanidine and acetylaminoantipyrine—may be explained by the dipolarity of the un-ionized molecules. With barbital, the two lipophilic ethyl groups are too small to compensate for the considerable dipolarity of the un-ionized barbituric acid ring; also it may be seen that barbital is appreciably ionized, which contributes to the relatively small permeability constant. Sulfaguanidine and acetylaminoantipyrine are both very polar molecules. Mecamylamine also might be considered an exception, since it shows a modest permeability even though strongly ionized; there is no dipolarity in mecamylamine except in the amino group.

Absorption of Drugs

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes that a drug may pass through in order to gain access to the extracellular fluid, it might be expected that the particular site of application (or *route*) would make little difference to the successful absorption of the drug. In actual fact, it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed. These factors are discussed in the following sections, along with an account of the ways that drug formulations may be manipulated to alter the ability of a drug to be absorbed readily.

Routes of Administration

Drugs may be administered by many different routes. The various routes include oral, rectal, sublingual or buccal, parenteral, inhalation and topical. The choice of a route depends upon both convenience and necessity.

Oral Route—This is obviously the most convenient route for access to the systemic circulation, providing that various factors do not militate against this route. Oral administration does not always give rise to sufficiently high plasma concentrations to be effective; some drugs are absorbed unpredictably or erratically; patients occasionally have an absorption malfunction. Drugs may not be given by mouth to patients with gastrointestinal intolerance, or who are in preparation for anesthesia or who have had gastrointestinal surgery. Oral administration also is precluded in coma.

Rectal Route—Drugs that ordinarily are administered by the oral route usually can be administered by injection or by the alternative *lower enteral* route, through the anal portal into the rectum or lower intestine. With regard to the latter, *rectal suppositories* or *retention enemas* formerly were used quite frequently, but their popularity has abated somewhat, owing to improvements in parenteral preparations. Nevertheless, they continue to be valid and, sometimes, very important ways of administering a drug, especially in pediatrics and geriatrics. In Fig 10[8] the availability of a drug by retention enema may be compared with that by the intravenous and oral route and rectal suppository administration. It is apparent that the retention enema may be a very satisfactory means of administration but that rectal suppositories may be inadequate where rapid absorption and high plasma levels are required. The illustration is not intended to lead the reader to the conclusion that a retention enema always will give more prompt and higher blood levels than the oral route, for converse findings for the same drug have been reported,[9] but, rather, to show that the retention enema may offer a useful substitute for the oral route.

Sublingual or Buccal Route—Even though an adequate plasma concentration eventually may be achievable by the oral route, it may rise much too slowly for use in some situations where a rapid response is desired. In such situations parenteral therapy usually is indicated. However, the patients with angina pectoris may get quite prompt relief from an acute attack by the *sublingual* or *buccal* administration of nitroglycerin, so that parenteral administration may be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route.

Parenteral Routes—These routes, by definition, include any route other than the oral-gastrointestinal (enteral) tract,

[illegible] acknowledge the co-operation of the surgical and gynaecological services of Stobhill General Hospital and Southern General Hospital, Glasgow.

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Received July 10, 1981

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rtical bars represent s.d. ▲ 30–40 mean 75 years, n = 8).

lewed the literature concerning n the sensitivity of animal aortae e evidence is conflicting. Carrier urated a decrease in sensitivity n the rat. Gray (1977) found an ty with age in the dog while 78) found no change with age in these studies involved immature as opposed to a comparison d senescent. The present study elderly subjects. There was no the sensitivity of human arterial aline. This is found when the ns is considered alone or when it non-receptor mediated contrac assium.

fics for these experiments had to ects with an underlying disease. to surgery, receiving medication adrenergic nervous system nor underlying arterial disease. Our ed by recent studies *in vivo* with eers (Elliot *et al.*, 1981) and with In young and old subjects).

an find no evidence *in vitro* that vascular α-adrenoceptor sensreasing age. Further studies will ermine whether changes in β- subtypes of α-adrenoceptors ardiovascular system.

BIOAVAILABILITY OF SUBLINGUAL ERGOTAMINE

Sublingual ergotamine has been used for years in the treatment of migraine attacks without any proof of its effectiveness. In a double-blind clinical trial no difference in relief was found between sublingual ergotamine and placebo (Crooks *et al.*, 1964). Similarly, a study on the buccal absorption of ergotamine indicated that it is unlikely for therapeutically useful amounts of drug to be absorbed across the buccal membrane (Sutherland *et al.*, 1974).

In contrast, Winsor (1981) in a nonblind cross-over study with finger-plethysmography found that the peripheral vasoconstrictory effect of ergotamine was equal after 0.25 mg intramuscularly or 2 mg sublingually, and significantly different from sublingual placebo. The two forms at these doses should thus be equally effective in migraine. With a high performance liquid chromatographic (h.p.l.c.) assay for ergotamine, with a detection level of 0.1 ng/ml in plasma (Edlund, 1981), we have investigated several administration forms of the drug. The results for sublingual ergotamine are reported as they cast serious doubt on the equipotency of sublingual and intramuscular forms of ergotamine.

Four volunteers (medical personnel, non-migraineurs) kept a sublingual tablet of 2 mg ergotamine tartrate (Lingraine®, Winthrop) under the tongue until dissolved. Blood was drawn after 5, 10, 20, 30, 60, 90 and 120 min. The samples were immediately centrifuged and kept deep frozen until analysed by the h.p.l.c. method. Ergotamine above the detection level was not found in any of the samples. Then the procedure was repeated in the same volunteers with another batch of Lingraine®. Again no ergotamine could be detected. The manufacturer informed us that both batches of Lingraine® were more than 2 years before their expiry date. For comparison we selected 4 migraine patients, who during the same period had their plasma levels of ergotamine determined with h.p.l.c. after 0.5 mg ergotamine tartrate/70 kg body weight intramuscularly. The mean and range of ergotamine levels in ng/ml plasma were after 30 min: 0.96 (0.48–1.41), after 60 min: 0.80 (0.57–1.07) and after 120 min: 0.57 (0.43–0.71). Even corrected to a dose of 0.25 mg the plasma levels of ergotamine are clearly above the detection level of 0.1 ng/ml.

These results were not obtained in a regular cross-over study. However, the discrepancy in plasma

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levels between sublingual and intramuscular ergotamine is so striking that it is unlikely for ergotamine 2 mg sublingually to have the same bioavailability as 0.25 mg intramuscularly.

Are the two forms of ergotamine then equipotent in their vasoconstrictory effect due to some active metabolites not measured by the specific h.p.l.c. method? Before going into speculations along these lines, we would suggest that the results with finger-plethysmography should be confirmed in a placebo-controlled double-blind study with direct measurements of the vasoconstrictory effect of ergotamine. Our main objection against the results with finger-plethysmography is that the effect of the reference form, intramuscular ergotamine, only had a duration of 90 min on venous occlusion blood flow. This short duration of action is not in agreement with recent investigations on arteries with ergotamine (Tfelt-Hansen *et al.*, 1980) and on veins with dihydroergotamine (Aellig, 1981). The duration of these ergot alkaloids vasoconstrictory effect in man was found to be at least 24 and 8 h respectively. Further, a dose-response curve for the biological effect should be established before the question of biological equipotency can be answered satisfactorily.

If proven to be equipotent to parenteral ergotamine in such studies, sublingual ergotamine should undergo a controlled clinical trial in migraine.

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Received July 27, 1981

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VERAPAMIL BIOAVAILABILITY AND DOSAGE IN LIVER DISEASE

May we be permitted to comment on the critical remarks made by Somogyi *et al.* (1981) on our dosage recommendations for verapamil and at the same time discuss the wider significance of verapamil dosage in liver disease.

Somogyi *et al.* (1981) recommend that the oral dose of verapamil in liver cirrhosis patients should be greatly reduced, and more so than required in the case of the intravenous dose. The oral dose they recommend is as little as one fifth of that used in patients with normal liver function. In our dosage recommendations, based on intravenous administration in patients with cirrhosis, hepatitis and fatty liver disease, a reduction to about one third was indicated, although there was considerable inter-patient variation (Woodcock *et al.*, 1979). Verapamil clearance data following oral treatment in liver patients were not available at this time. Somogyi *et al.* (1981) state that we 'failed to appreciate the difference between oral and intravenous clearance of verapamil' and thus imply that we were erroneous in the interpretation of our observations. This statement, apart from being incorrect (the first pass effect of verapamil is common knowledge since the report of Shomerus *et al.* (1976)) misses the fundamental point which is that the large reduction, to one fifth, in the oral dose of verapamil recommended by themselves, applies only to liver cirrhosis patients who have marked intra- and extra-hepatic shunts. This fact was omitted from their discussion.

We have reported observations on liver cirrhosis patients in whom the bioavailability of verapamil was the same as in healthy subjects despite a greatly reduced systemic clearance (Woodcock *et al.*, 1981). In patients with fatty liver the first pass extraction was increased and the bioavailability actually lower than normal. A higher than normal extraction of verapamil is, according to Wilkinson & Shand (1975), to be expected when the rate of blood flow through the liver is reduced. In these patients there was thus no evidence for the development of hepatic shunts and a dosage reduction of the magnitude suggested by

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Tenth Edition

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Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. 10/e

1234567890 DOWDOW 0987654321

ISBN 0-07-135469-7

This book was set in Times Roman by York Graphic Services, Inc. The editors were Martin J. Wonsiewicz and John M. Morriss; the production supervisor was Philip Galea; and the cover designer was Marsha Cohen/Parallelogram. The index was prepared by Irving Condé Tullar and Coughlin Indexing Services, Inc.
R.R. Donnelley and Sons Company was printer and binder.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Goodman and Gilman's the pharmacological basis of therapeutics.—10th ed. / [edited by]
Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-07-135469-7
1. Pharmacology. 2. Chemotherapy. I. Title: Pharmacological basis of therapeutics.
II. Goodman, Louis Sanford III. Gilman, Alfred IV. Hardman, Joel G.
V. Limbird, Lee E. VI. Gilman, Alfred Goodman
[DNLM: 1. Pharmacology. 2. Drug Therapy. QV 4 G6532 2002]
RM300 G644 2001
615'.7—dc21 2001030728

INTERNATIONAL EDITION ISBN 0-07-112432-2

tone is low (Marshall *et al.*, 1987; Hanel and Lands, 1982). Further, acetaminophen does not inhibit neutrophil activation as do other NSAIDs (Abramson and Weissmann, 1989).

Single or repeated therapeutic doses of acetaminophen have no effect on the cardiovascular and respiratory systems. Acid–base changes do not occur, nor does the drug produce the gastric irritation, erosion, or bleeding that may occur after administration of salicylates. Acetaminophen has no effects on platelets, bleeding time, or the excretion of uric acid.

Pharmacokinetics and Metabolism. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes, and the half-life in plasma is about 2 hours after therapeutic doses. Acetaminophen is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; only 20% to 50% may be bound at the concentrations encountered during acute intoxication. After therapeutic doses, 90% to 100% of the drug may be recovered in the urine within the first day, primarily after hepatic conjugation with glucuronic acid (about 60%), sulfuric acid (about 35%), or cysteine (about 3%); small amounts of hydroxylated and deacetylated metabolites also have been detected. Children have less capacity for glucuronidation of the drug than do adults. A small proportion of acetaminophen undergoes cytochrome P450–mediated *N*-hydroxylation to form *N*-acetyl-benzoquinoneimine, a highly reactive intermediate. This metabolite normally reacts with sulfhydryl groups in glutathione. However, after ingestion of large doses of acetaminophen, the metabolite is formed in amounts sufficient to deplete hepatic glutathione (*see* below).

Therapeutic Uses. Acetaminophen is a suitable substitute for aspirin for analgesic or antipyretic uses; it is particularly valuable for patients in whom aspirin is contraindicated (*e.g.*, those with peptic ulcer) or when the prolongation of bleeding time caused by aspirin would be a disadvantage. The conventional oral dose of acetaminophen is 325 to 1000 mg (650 mg rectally); the total daily dose should not exceed 4000 mg. For children, the single dose is 40 to 480 mg, depending upon age and weight; no more than five doses should be administered in 24 hours. A dose of 10 mg/kg also may be used.

Toxic Effects. In recommended therapeutic dosage, acetaminophen usually is well tolerated. Skin rash and other allergic reactions occur occasionally. The rash is usually erythematous or urticarial, but sometimes it is more serious and may be accompanied by drug fever and mucosal lesions. Patients who show hypersensitivity reactions to the salicylates only rarely exhibit sensitivity to acetaminophen. In a few isolated cases, the use of acetaminophen has been associated with neutropenia, thrombocytopenia, and pancytopenia.

The most serious adverse effect of acute overdosage of acetaminophen is a dose-dependent, potentially fatal hepatic necrosis (*see* Thomas, 1993). Renal tubular necrosis and hypoglycemic coma also may occur. The mechanism by which overdosage with acetaminophen leads to hepatocellular injury and death involves its conversion to a toxic reactive metabolite (*see also* Chapter 4). Minor pathways of acetaminophen elimination are *via* conjugation with glucuronide and sulfate. The major pathway of metabolism is *via* cytochrome P450s to the intermediate, *N*-acetyl-*para*-benzoquinonimino, which is very electrophilic. Under normal circumstances, this intermediate is inated by conjugation with glutathione (GSH) and the metabolized to a mercapturic acid and excreted into ... However, in the setting of acetaminophen overdose, h... lular levels of GSH become depleted. Two consequence... as result of depletion of GSH. Since GSH is an importa... in antioxidant defense, hepatocytes are rendered highly ... ble to oxidant injury. Depletion of GSH also allows the ... intermediate to bind covalently to cell macromolecules ... to dysfunction of enzymatic systems.

Hepatotoxicity. In adults, hepatotoxicity may occur ... gestion of a single dose of 10 to 15 g (150 to 250 mg... acetaminophen; doses of 20 to 25 g or more are potenti... tal. Alcoholics can have hepatotoxicity with much lower... even with doses in the therapeutic range. The mechan... this effect is discussed above (*see also* Chapter 4). Sym... that occur during the first 2 days of acute poisoning b... aminophen may not reflect the potential seriousness of the... ication. Nausea, vomiting, anorexia, diaphoresis, and abd... pain occur during the initial 24 hours and may persis... week or more. Clinical indications of hepatic damage, ... manifest within 2 to 4 days of ingestion of toxic doses; ... aminotransferases are elevated (sometimes markedly ... the concentration of bilirubin in plasma may be increa... addition, the prothrombin time is prolonged. Perhaps ... poisoned patients who do not receive specific treatment ... severe liver damage; of these, 10% to 20% eventually ... hepatic failure. Acute renal failure also occurs in some p... Biopsy of the liver reveals centrilobular necrosis with ... of the periportal area. In nonfatal cases, the hepatic lesio... reversible over a period of weeks or months.

Severe liver damage (with levels of aspartate amino... ferase activity in excess of 1000 IU per liter of plasma) oc... 90% of patients with plasma concentrations of acetamino... greater than 300 μg/ml at 4 hours or 45 μg/ml at 15... after the ingestion of the drug. Minimal hepatic damage ... anticipated when the drug concentration is less than 120 ... at 4 hours or 30 μg/ml at 12 hours after ingestion. Th... tential severity of hepatic necrosis also can be predicted ... the half-life of acetaminophen observed in the patient; ... greater than 4 hours imply that necrosis will occur, while ... greater than 12 hours suggest that hepatic coma is likely... nomogram provided in Figure 27–2 relates the plasma lev... acetaminophen and time after ingestion to the predicted se... of liver injury (*see* Rumack *et al.*, 1981).

Early diagnosis is vital in the treatment of overdosage ... acetaminophen, and methods are available for the rapid det... nation of concentrations of the drug in plasma. However, th... should not be delayed while awaiting laboratory results ... history suggests a significant overdosage. Vigorous suppo... therapy is essential when intoxication is severe. Gastric l... should be performed in all cases, preferably within 4 hou... the ingestion.

The principal antidotal treatment is the administrati... sulfhydryl compounds, which probably act, in part, by repla... ing hepatic stores of glutathione. *N-acetylcysteine* (MUCO... MUCOSIL) is effective when given orally or intravenously... intravenous form is available in Europe, where it is consid... the treatment of choice. When given orally, the *N*-acetylcys... solution (which has a foul smell and taste) is diluted with ...

Table A–II–1
PHARMACOKINETIC DATA

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
ABACAVIR[a] (Chapter 51)							
83 (63–110)	1 (0–4)	—	12.8 (9.3–17.5)	0.84 (0.69–1.03)	1.0 (0.8–1.3)	Tab: 0.63 (0.4–1.1)[b] Sol: 0.5 (0.5–0.6)[b]	Tab: 2.6 (2.3–2.9) μg/ml[b] Sol: 2.9 (2.5–3.4) μg/ml[b]
ACETAMINOPHEN[a] (Chapter 27)							
88 ± 15 ⟷ Child	3 ± 1 ⟷ Neo, Child	<20	5.0 ± 1.4[b] ↓ Hep[c] ⟷ Aged, Child ↑ Obes, HTh, Preg	0.95 ± 0.12[b] ⟷ Aged, Hep[c] LTh, HTh, Child	2.0 ± 0.4 ⟷ RD, Obes, Child ↑ Neo, Hep[c] ↓ HTh, Preg	0.33–1.4[d]	20 μg/ml[e]
(L)-α-ACETYLMETHADOL (LAAM)[a] (Chapter 23)							
47 ± 5	6	80	4.93 ± 0.58	7.0	L: 18.5 ± 4.9 NL: 23.9 ± 3.2 DL: 65.8 ± 10.1	L: 2.6 ± 0.2[b] NL: 3.9 ± 0.7[b] DL: 31 ± 9.6[b]	L: 63 ± 8 ng/ml[b] NL: 44 ± 4 ng/ml[b] DL: 19 ± 1 ng/ml[b]
ACETYLSALICYLIC ACID[a] (Chapters 27, 55)							
68 ± 3 ⟷ Aged, Cir	1.4 ± 1.2	49 ↓ RD	9.3 ± 1.1 ⟷ Aged, Cir	0.15 ± 0.03	0.25 ± 0.03 ⟷ Hep	0.39 ± 0.21[b]	24 ± 4 μg/ml[b]

[a]Data from male subjects with HIV infection. Values are geometric means and 95% CI. Metabolized by ADH, UGT, and other enzymes.
[b]C_{max} and T_{max} (geometric mean and 95% CI) following a 300-mg oral tablet (Tab) or solution (Sol).

References: Barry, M., Mulcahy, F., Merry, C., Gibbons, S., and Back, D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. *Clin. Pharmacokinet.*, 1999, *36*:289–304.
Chittick, G.E., Gillotin, C., McDowell, J.A., Lou, Y., Edwards, K.D., Prince, W.T., and Stein, D.S. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. *Pharmacotherapy*, 1999, *19*:932–942.

[a]Values reported are for a linear kinetic model for doses less than 2 g; drug exhibits concentration-dependent kinetics above this dose.
[b]Assuming a 70-kg body weight; reported range, 65 to 72 kg.
[c]Acetaminophen-induced hepatic damage or acute viral hepatitis.
[d]Absorption rate, but not extent, depends on gastric emptying; hence, slowed after food as well as in some disease states and cotreatment with drugs that cause gastroparesis.
[e]Mean concentration following a 20-mg/kg oral dose. Hepatic toxicity associated with levels >300 μg/ml at 4 hours after an overdose.

Reference: Forrest, J.A., Clements, J.A., and Prescott, L.F. Clinical pharmacokinetics of paracetamol. *Clin. Pharmacokinet.*, 1982, *7*:93–107.

[a]Data from healthy adult male subjects. LAAM (L) is metabolized by cytochrome P450 (primarily CYP3A) to active metabolites, nor-LAAM (NL) and dinor-LAAM (DL).
[b]Following a single 40-mg oral dose.

References: Kaiko, R.F., Chatterjie, N., and Inturrisi, C.E. Simultaneous determination of acetylmethadol and its active biotransformation products in human biofluids. *J. Chromatogr.*, 1975, *109*:247–258.
Walsh, S.L., Johnson, R.E., Cone, E.J., and Bigelow, G.E. Intravenous and oral *l*-α-acetylmethadol: pharmacodynamics and pharmacokinetics in humans. *J. Pharmacol. Exp. Ther.*, 1998, *285*:71–82.

[a]Values given are for unchanged parent drug. Acetylsalicylic acid is converted to salicylic acid during and after absorption (Cl and $t_{1/2}$ of salicylate are dose-dependent; half-life varies between 0.4 hours after a 300-mg dose to 19 hours when there is intoxication).
[b]Oral dosing given to adults.

Reference: Roberts, M.S., Rumble, R.H., Wanwimolruk, S., Thomas, D., and Brooks, P.M. Pharmacokinetics of aspirin and salicylate in elderly subjects and in patients with alcoholic liver disease. *Eur. J. Clin. Pharmacol.*, 1983, *25*:253–261.

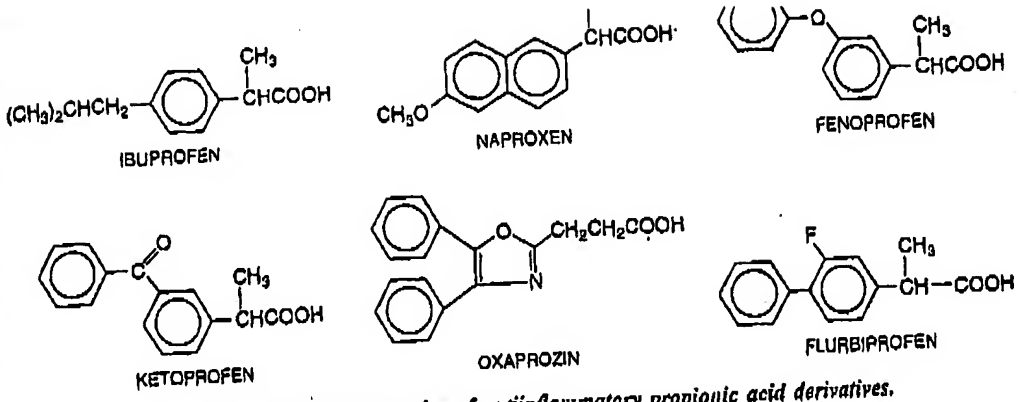

Figure 27–3. Structural formulas of antiinflammatory propionic acid derivatives.

ith this drug is greater. It is available for sale without a prescription in the United States. Naproxen has a onger half-life than most of the other structurally and unctionally similar agents, making twice-daily administration of it feasible. This drug also is available without prescription in the United States. Oxaprozin also has a ong half-life and can be given once daily. The structural ormulas of these drugs are shown in Figure 27–3.

Pharmacological Properties. The pharmacodynamic roperties of the propionic acid derivatives do not differ ignificantly. All are effective cyclooxygenase inhibitors, although there is considerable variation in their potency. For example, naproxen is approximately 20 times more potent than aspirin, while ibuprofen, fenoprofen, and aspirin are roughly equipotent as cyclooxygenase inhibitors. All of these agents alter platelet function and prolong bleeding time, and it should be assumed that any patient who is intolerant of aspirin also will experience a severe reaction after administration of one of these drugs. Some of the propionic acid derivatives have prominent inhibitory effects on leukocyte function; naproxen is particularly potent in this regard. While the compounds do vary in potency, this is not of obvious clinical significance. All are effective antiinflammatory agents in various experimental animal models of inflammation; all have useful antiinflammatory, analgesic, and antipyretic activities in human beings. Although all of these compounds can cause gastric toxicity in patients, these are usually less severe than with aspirin.

It is difficult to find data on which to base a rational choice among the members of the propionic acid derivatives, if in fact one can be made. However, in relatively small clinical studies that compared the activity of several members of this group, patients preferred naproxen in terms of analgesia and relief of morning stiffness (*see* Huskisson, *in* Symposium, 1983a; Hart and Huskisson, 1984). With regard to side effects, naproxen was the best tolerated, followed by ibuprofen and fenoprofen. There was considerable interpatient variation in the preference for a single drug and also between the designations of the best and the worst drug. Unfortunately, it is probably impossible to predict *a priori* which drug will be most suitable for any given individual. Nevertheless, more than 50% of patients with rheumatoid arthritis probably will achieve adequate symptomatic relief from the use of one or another of the propionic acid derivatives, and many clinicians favor their use instead of aspirin in such patients.

Drug Interactions. The potential adverse drug interactions of particular concern with propionic acid derivatives result from their high degree of binding to albumin in plasma. However, the propionic acid derivatives do not alter the effects of the oral hypoglycemic drugs or warfarin. Nevertheless, the physician should be prepared to adjust the dosage of warfarin because these drugs impair platelet function and may cause gastrointestinal lesions.

Ibuprofen

Ibuprofen is supplied as tablets containing 200 to 800 mg; the 200-mg tablets (ADVIL, NUPRIN, others) are available without a prescription.

For rheumatoid arthritis and osteoarthritis, daily doses up to 3200 mg in divided portions may be given, although usual total dose is 1200 to 1800 mg. It also may be possible to reduce the dosage for maintenance purposes. For mild moderate pain, especially that of primary dysmenorrhea, usual dosage is 400 mg every 4 to 6 hours as needed. The drug may be given with milk or food to minimize gastrointestinal side effects. Ibuprofen has been discussed in detail by Kantor (1979) and by Adams and Buckler (*in* Symposium, 1983a).

Pharmacokinetics and Metabolism. Ibuprofen is rapidly absorbed after oral administration, and peak concentration

Table A–II–1
PHARMACOKINETIC DATA (*Continued*)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	PEAK TIME (*hours*)	PEAK CONCENTRATIONS
HYDROMORPHONE[a] (Chapter 23)							
Oral: 42 ± 23 SC: ~80	6	7.1	14.6 ± 7.6	2.90 ± 1.31[b]	2.4 ± 0.6	IV: –[c] Oral: 1.1 ± 0.2[c]	IV: 242 ng/ml[c] Oral: 11.8 ± 2.6 ng/ml[c]
HYDROXYUREA[a,2] (Chapter 52)							
108 ± 18 (79–108)	35.8 ± 14.2	Negligible	72 ± 17 ml · min^{-1} (m^2)$^{-1}$[b] (36.2–72.3)	19.7 ± 4.6 l/m^2	3.4 ± 0.7 (2.8–4.5)	IV: 0.5[c] Oral: 1.2 ± 1.2[c]	IV: 1007 ± 371 μM[c] Oral: 794 ± 241 μM[c]
IBUPROFEN[a] (Chapter 27)							
~80	<1	>99[b] ↔ RA, Alb	0.75 ± 0.20[b,c] ↑ CF ↔ Child, RA	0.15 ± 0.02[c] ↑ CF	2 ± 0.5[b] ↔ RA, CF, Child ↑ Cirr	1.6 ± 0.3[d]	61.1 ± 5.5 μg/ml[d]

[a]Data from healthy male subjects. Extensively metabolized. The principal metabolite, 3-glucuronide, accumulates to much higher (27-fold) levels than parent drug, and may contribute to some side effects (not antinociceptive).

[b]V_{area} reported.

[c]Following a single 2-mg IV (bolus, sample at 3 minutes) or 4-mg oral dose.

References: Hagen, N., Thirlwell, M.P., Dhaliwal, H.S., Babul, N., Harsanyi, Z., and Darke, A.C. Steady-state pharmacokinetics of hydromorphone and hydromorphone-3-glucuronide in cancer patients after immediate and controlled-release hydromorphone. *J. Clin. Pharmacol.*, 1995, *35*:37–44.

Moulin, D.E., Kreeft, J.H., Murray-Parsons, N., and Bouquillon, A.I. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet*, 1991, *337*:465–468.

Parab, P.V., Ritschel, W.A., Coyle, D.E., Gregg, R.V., and Denson, D.D. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm. Drug Dispos.*, 1988, *9*:187–199.

[a]Data from male and female patients treated for solid tumors. A range of mean values from multiple studies is shown in parenthesis.

[b]Nonrenal elimination of hydroxyurea is thought to exhibit saturable kinetics through a 10- to 50-mg/kg dose range.

[c]Following a single 2-g, 30-minute intravenous infusion or oral dose.

References: Gwilt, P.R., and Tracewell, W.G. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin. Pharmacokinet.*, 1998, *34*:347–358.

Rodriguez, G.I., Kuhn, J.G., Weiss, G.R., Hilsenbeck, S.G., Eckardt, J.R., Thurman, A., Rinaldi, D.A., Hodges, S., Von Hoff, D.D., and Rowinsky E.K. A bioavailability and pharmacokinetic study of oral and intravenous hydroxyurea. *Blood*, 1998, *91*:1533–1541.

[a]Racemic mixture. Kinetic parameters for the active *S*-(+)-enantiomer do not differ from those for the inactive *R*-(−)-enantiomer when administered separately; 63 ± 6% of the *R*-(−)-enantiomer undergoes inversion to the active isomer.

[b]Unbound percent of *S*-(+)-ibuprofen (0.77 ± 0.20%) is significantly greater than that of *R*-(−)-ibuprofen (0.45 ± 0.06%). Binding of each enantiomer is concentration dependent and is influenced by the presence of the optical antipode, leading to nonlinear elimination kinetics.

[c]*CL/F* and V_{ss}/F reported.

[d]Following a single 800-mg dose of racemate. A level of 10 μg/ml provides antipyresis in febrile children.

References: Lee, E.J., Williams, K., Day, R., Graham, G., and Champion, D. Stereoselective disposition of ibuprofen enantiomers in man. *Br. J. Clin. Pharmacol.*, 1985, *19*:669–674.

Lockwood, O.F., Albert, K.S., Gillespie, W.R., Bole, G.G., Harkcom, T.M., Szonan, G.J., and Wagner, J.G. Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. *Clin. Pharmacol. Ther.*, 1983, *34*:97–103.